ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Ergot Alkaloids, Separation of. H. Hellberg. (*Farm. Revy.*, 1954, **53**, 605.) Partition coefficients between phosphate buffers and benzene were determined for dihydroergotamine, dihydroergocornine, dihydroergokryptine and dihydroergocristine. Systematic extraction does not permit separation of mixtures of these alkaloids. The *p*H partition curves were used to calculate the maxima of the Craig distribution curves, and these were afterwards verified experimentally. The partition of methylergometrine between phosphate buffers and ether was determined similarly. The results indicate that with the aid of a Craig distribution through 30 units it is possible to identify and separate methylergometrine, ergometrine and ergometrinine. J. B. S.

ANALYTICAL

Isoniazid, Determination of. E. Kühni, M. Jacob and H. Grossglauser. (*Pharm. Acta Helvet.*, 1954, **29**, 233.) Methods for the titration of isoniazid, using potassium iodate or iodine, give low results, but potassium bromate is more satisfactory. The method is as follows: 0·2 g. of the compound is dissolved in 30 ml. of water and treated with 75 ml. of 25 per cent. hydrochloric acid, and titrated with 0·5N potassium bromate solution (added at 3 to 4 ml. per minute), using *p*-ethoxychrysoidine as indicator. The end-point is shown by a yellow colour: 1 ml. of bromate solution corresponds to 0·01714 g. of isoniazid. Potentiometric titration of isoniazid with perchloric acid may be carried out after acetylation: 0·15 g. of dried isoniazid is dissolved in 20 ml. of acetic anhydride-acetic acid (1:9) and titrated potentiometrically or visually (crystal violet as indicator) with 0·1N perchloric acid in glacial acetic acid. There is a slight difference in the factor according to the method of detecting the end-point, and this should be determined. G. M.

Morphine, Behaviour of, on Ion Exchange Resins,. E. E. Hamlow, H. G. DeKay and E. Ramstad. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 460.) Chromatographic columns were packed with resin particles of suitable size, back-washed and regenerated with a 10 per cent. solution of hydrochloric acid for cation exchangers or 4 per cent. sodium hydroxide or carbonate for anion exchangers. Solutions of morphine sulphate were passed through the columns which were then washed and the alkaloid eluted, the morphine being determined in the eluate by carrying out the nitrosomorphine reaction and measuring the colour at 442 mμ. Amberlite IR-120 (strong cationic exchanger) absorbed morphine quantitatively and the alkaloid was completely recovered by elution with 4N methanolic ammonium hydroxide. The weak cationic exchanger Amberlite IRC-50 did not effectively absorb morphine from morphine sulphate solution, but the alkaloid was removed quantitatively from a methanolic solution of the base passed through a column of resin in the hydrogen form. The alkaloid was eluted completely with N hydrochloric acid or 4N methanolic

ammonium hydroxide. Amberlite IR-4B (weak anionic exchanger) readily separated morphine from a solution of its sulphate. Methanol (75 per cent.) was used as solvent to prevent the formation of a precipitate of morphine in the column, and methanol was used to wash the liberated alkaloid from the column. Amberlite IRA-400 and Nalcite SAR (strong anionic exchangers) removed morphine completely from a methanolic solution and the alkaloid could be eluted completely with N hydrochloric acid. Duolite C-60 (weak cationic exchanger) and Ionac A-300 (anionic exchanger of intermediate strength) were not suitable for the quantitative separation of morphine from solutions. For the separation of mixtures of morphine with papaverine and narcotine, Amberlite IR-4B or IR-120 was used together with IRA-400, which absorbs morphine but not the non-phenolic alkaloids. The morphine recovered was only slightly impure, as shown by examination of the ultra-violet absorption spectrum. In the analysis of tincture of opium, some colouring matter was eluted with the morphine and interfered with the determination. G. B.

Vitamin A in Liver, Determination of. A. R. Ames, H. A. Risley and P. L. Harris. (*Analyt. Chem.*, 1954, **26**, 1378.) A simplified procedure has been developed for the determination of vitamin A in liver tissue, involving the drying of the liver by grinding with anhydrous sodium sulphate, the addition of ethyl ether, and the determination of the vitamin A content of an aliquot by means of the antimony trichloride reaction. Tables are given showing the recovery of known amounts of vitamin A added to rat livers. The standard deviation of a single determination was $\pm$ 2·4 per cent. with a standard error of 0·56 per cent. (19 values). An examination of three other methods of vitamin A estimation showed that all methods have a comparable precision. R. E. S.

PLANT ANALYSIS

Opium, Determination of the Origin of. J. C. Bartlet and C. G. Farmilo. (*Nature, Lond.*, 1954, **174**, 407.) The ash of more than one hundred opium samples from Yugoslavia, Turkey, Iran, India, Indo-China, Korea and China has been analysed for both major and minor constituents. Potassium, calcium, phosphorus, sodium, magnesium, silicon, iron, aluminium, titanium, boron, manganese, molybdenum, lead, tin and copper by spectrographic, colorimetric and flame photometric procedures. The relationships between the calcium and potassium content is largely characteristic of the geographical origin. Indian samples have a high potassium and low calcium content in the ash. The druggist type of Turkish opium has a high calcium and low potassium content. Far Eastern samples have a high phosphorus content. Iranian opium samples have ashes with relatively high tin and copper content. The ash of Turkish opiums can be distinguished from that of Yugoslavian and Indian opium by their low silicon and iron content. Yugoslavian opium has ash with calcium and potassium content similar to that of some Indian samples, but may be distinguished by a lower phosphorus content. J. B. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

"Bound" Morphine, Isolation and Identification of. R. A. Seibert, C. E. Williams and R. A. Huggins. (*Science*, 1954, **120**, 222.) Morphine is excreted in the urine in the free form and in a bound form believed to be with

glucuronic acid. Urine collected from anæsthetised dogs infused with morphine was treated with urease to remove urea and evaporated to a small volume. The concentrated urine was chromatographed on Whatman No. 1 filter paper with an *n*-butanol, acetic acid and water solution. Spraying with Munier's alkaloid reagent gave a white spot with an R_F of 0·16 to 0·20 and a higher spot with an R_F of 0·55 to 0·60 corresponding to morphine. The lower spot was extracted with absolute methanol and then eluted with water when a pure compound was obtained by recrystallising from methanol and water. The pure compound was hydrolysed in two ways, (*a*) with β-glucuronidase and (*b*) by autoclaving. Chromatography of the resultant solutions gave a spot identical with morphine and a spot corresponding to glucuronic acid. A middle spot which was also obtained has not been identified. It is concluded that the excretion product of morphine is a glucuronide, the structure of which is being investigated.

G. F. S.

BIOCHEMICAL ANALYSIS

Filter Paper Electrophoresis, A Rapid Method for. S. D. Vesselinovitch and H. S. Funnell. (*Canad. J. Biochem. Physiol.*, 1954, **32**, 567.) An improved technique is described for filter paper electrophoresis in which the running time is reduced to two hours. It is useful in the detection of qualitative and quantitative changes occurring among the plasma proteins during disease. Strips of Whatman No. 1 filter paper (28 by 4 cm.) are saturated with barbiturate buffer, *p*H 8·6, with an ionic strength of 0·05. Excess buffer is removed and the strips are horizontally placed on a nylon brush support with their ends hanging free. The support is transferred to a special plastic electrophoretic chamber and the overhanging ends of the strips are submerged a few mm. into the buffer in the side vessels. Serum (0·005 to 0·01 ml.) is evenly applied by a micropipette along a line across the strip 1·5 cm. from its centre towards the negative pole. The chamber is then closed and the current (potential gradient 12 to 14 v./cm.) is switched on for two hours. The strips are then removed and dried for 10 minutes in an oven at 120° C. The dried strips are stained for 5 minutes with a 1 per cent. solution of bromphenol blue in ethanol saturated with mercuric chloride, and washed in repeated changes of 0·2 per cent. acetic acid solution until no yellow colour appears in the wash. The faintly stained yellow strips are then placed in ethanol for 2 minutes when the yellow is converted to an intense blue. The intensely coloured protein fractions are easily interpreted with the naked eye. Electrophoretic patterns of 5 dog and one human serum are illustrated.

G. F. S.

Vitamin B_{12}, Microbiological Determination of. F. J. Bandelin and J. V. Tuschoff. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 474.) The following method is simpler and more rapid than the microbiological assay using *Lactobacillus leichmanii* as the test organism, and gives comparable results with good reproducibility for samples of desiccated liver, liver injection and various liver fractions. To each of a series of tubes containing a sample under test, add 5 ml. of double strength Burkholder's medium and water to 10 ml. Autoclave for 5 minutes at 110° C. and cool rapidly by immersion in cold water so as to avoid discoloration of the medium. Inoculate each tube with a drop of freshly prepared suspension of *E. coli* mutant 113–3 and incubate at 32° C. for 15–18 hours. Assess growth by measurement of the turbidity using a spectrophotometer set

at 650 mμ with no filter. Shaking of the tubes during incubation should be avoided as a steeper growth-response curve is obtained and maximum growth is reached more rapidly than when aeration is allowed to occur. Methionine interferes in the determination if present in a concentration more than 70,000 times that of the cyanocobalamin. G. B.

CHEMOTHERAPY

Antifungal Compounds, New Series of. E. B. Hodge, J. R. Hawkins and E. Kropp. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 501.) 16 compounds of the type Ar·CH(OR)·CX(NO_2)·R′ were prepared where Ar = phenyl, 2- or 4-chlorophenyl, 2:4- or 3:4-dichlorophenyl, furyl or *p*-anisyl, R = methyl, ethyl or 2-hydroxyethyl, R′ = ethyl, methyl or *n*-propyl and X = bromine. The antifungal activity was assessed by determining the minimum concentration of each substance which, added to Sabouraud's agar with added malt extract and poured into plates, inhibited the growth of fungi applied as a streak of cell suspension. The plates were examined for growth after incubation at 25° C. for 5 days. All the compounds were effective against *Aspergillus niger*, *Trichophyton mentagrophytes* and *Candida albicans*. Substitution in the aryl group generally had the effect of lowering the antifungal activity. On account of its effectiveness and relative ease of preparation, 2-bromo-1-methoxy-2-nitro-1-phenylpropane was selected for further trial. It proved effective in concentrations varying from 1 to 100 μg./ml. against a variety of yeasts and fungi. An ointment containing 1 per cent. of the substance in soft paraffin or vanishing cream base caused little or no irritation when applied daily to the skin of rabbits for a week, and preliminary results of clinical trials indicate that it may be of value in the treatment of *Trichophyton rubrum* infections. G. B.

Autonomic Ganglionic Blocking Agents Derived from Nicotine. A. P. Phillips. (*J. Amer. chem. Soc.*, 1954, **76**, 2211.) In a search for new useful hypotensive drugs among ganglionic blocking agents, the nicotine molecule has been modified. Treatment of nicotine with a series of alkyl halides gave di-quaternary ammonium salts. Catalytic hydrogenation, using Adams catalyst, of these salts and nicotine salts gave a series of di-tertiary amines and a di-secondary amine respectively. Reaction of one of the di-tertiary amine reduction products with several alkyl halides gave a new series of the di-quaternary ammonium salts. The di-quaternary ammonium salts of nicotine had no useful pharmacological actions. All the di-secondary and di-tertiary amines as well as their di-quaternary ammonium salts possessed marked hypotensive action. These compounds are derivatives of 3-(4′-aminobutyl)-piperidine. A. H. B.

β-Diethylaminoethyl Esters of ββ-Diphenylglycidic, ββ-Diphenyllactic and ββ-Diphenylglycenic Acids, as Antispasmodics. F. F. Blicke and J. A. Faust. (*J. Amer. chem. Soc.*, 1954, **76**, 3156.) The preparation of the β-diethylaminoethyl esters of ββ-diphenylglycidic, ββ-diphenyllactic and ββ-diphenylglycenic acids is described. The maximum effective dilution of these esters against the action of acetylcholine upon isolated intestine was 1:1,000,000. A. H. B.

β-Diethylaminoethyl Esters of Substituted Lactic and Acrylic Acids as Antispasmodics. F. F. Blicke and J. A. Faust. (*J. Amer. chem. Soc.*, 1954, **76**, 3159.) The preparation of β-diethylaminœthyl esters of α: β: β-diphenyllactic,

α : β : β-triphenylacrylic, α-methyl-β : β-diphenylactic and α-bromo-β : β-diphenylacrylic acids is described. The maximum effective dilution for the latter two esters was 1 : 3,000,000 and 1 : 1,000,000 respectively when tested against acetylchlorine-induced spasm of the isolated intestine. A. H. B.

PHARMACY

NOTES AND FORMULÆ

Alphaprodine Hydrochloride (Nisentil Hydrochloride). (*New and Non-offical Remedies, J. Amer. med. Ass.*, 1954, **155**, 1159.) Alphaprodine hydrochloride is 1 : 3-dimethyl-4-phenyl-4-piperidyl propionate hydrochloride. It is a white crystalline bitter powder with an amine-like odour, m.pt. 218° to 221° C., freely soluble in ethanol, chloroform, and water, and very slightly soluble in ether; a 1 per cent. solution has *p*H 4·5 to 5·2. It is stable to air, light, and heat. When treated with sulphuric acid containing a drop of formaldehyde, it gives an oranged-red colour. It yields a picrate melting at 213° to 218° C. When dried at 105° C. for 4 hours, the loss in weight does not exceed 0·5 per cent.; sulphated ash, not more than 0·1 per cent.; limit of heavy metals, 20 p.p.m. It contains 85·1 to 90·4 per cent. of alphaprodine, equivalent to 97 to 103 per cent. of the hydrochloride, and is assayed by extracting the base from alkaline solution with ether, dissolving it in hydrochloric acid, and titrating with sodium hydroxide, using methyl red as indicator. It is a short-acting narcotic analgesic. G. R. K.

Phenobarbitone, Soluble, Stability of Aqueous Solutions of. G. C. Walker and P. F. Gray. (*Canad. med. Ass. J.*, 1954, **71**, 8.) The stability of soluble phenobarbitone solutions in water, in diluted propylene glycol, and in water containing syrup of orange or aromatic elixir was determined at 4° C., 22° C. and 30° C. during periods of 1 to 8 weeks. The concentrations examined varied from 15 to 1200 mg. per 100 ml. At 4° C. decomposition occurred only in the solutions containing 1200 mg./100 ml. and then only to the extent of 2 per cent. in 8 weeks. Raising the temperature increased the rate of deterioration; the addition of syrup of orange or aromatic elixir appeared to decrease it slightly. Propylene glycol had no significant effect on stability. Growth of a fungus occurred mainly in the simple aqueous solutions, especially in those where concentration, temperature and period of observation were at a maximum. H. T. B.

Tablet Coatings, Cellulosic High Polymers as. D. W. Doerr, E. R. Serles and D. L. Deardorff. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 433.) Compressed tablets were given a prime coat of shellac, followed by 5 coats of hydroxyethylcellulose or sodium carboxymethylcellulose, applied as a 5 per cent. solution in ethanol (50 per cent.), in a coating pan. Each coat was allowed to dry for 4 to 5 minutes before completing the process with the aid of hot air for up to 1 minute. Tablets were aged for 4 hours at room temperature, and then polished by the application of a wax coating. Coatings were relatively thin, retaining closely the shape of the original tablet and not obscuring any grooves or embossed designs. The finished products showed less weight variation than commercial sugar-coated tablets. The disintegration time of the uncoated tablets (U.S. Pharmacopeia method) was increased only 20 seconds by the application of the coatings. The coated tablets were more resistant to

high temperature and humidity than sugar-coated tablets and less affected by infra-red heating and shaking tests. The coating process affects a considerable saving in time and labour over the conventional sugar-coating method. Colours may readily be incorporated in the coating, which can be applied successfully to enteric-coated tablets. G. B.

Tolazoline Hydrochloride (Priscoline Hydrochloride). (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1954, **155**, 445.) Tolazoline hydrochloride, 2-benzyl-2-imidazoline hydrochloride, $C_6H_5.CH_2.C_3H_5N_2,HCl$, is a white or slightly off-white, bitter powder with a slight aromatic odour; m.pt. 173° to 176° C., freely soluble in ethanol, chloroform, and water, and very slightly soluble in ether and ethyl acetate; *p*H of a 2·5 per cent. solution, 4·9 to 5·3. It is identified by preparing the picrate, which has a m.pt. of 145° to 149° C., and complies with a limit test for sulphate. When dried at 60° in vacuo for 4 hours, the loss in weight does not exceed 0·5 per cent.; sulphated ash, not more than 0·1 per cent. It contains 79·8 to 83·1 per cent. of tolazoline, when assayed by extraction with ether, solution in sulphuric acid, and titration of the excess of acid. It is also assayed for chloride by the addition of an excess of silver nitrate and titration with ammonium thiocyanate; the amount of chloride is 17·7 to 18·4 per cent., equivalent to 98·0 to 102·0 per cent. of tolazolin hydrochloride. Tolazoline hydrochloride is an adrenolytic, sympatholytic, and vasodilator drug. G. R. K.

PHARMACOGNOSY

Anthraglucosides, Localisation of, in Chinese Rhubarb. F. H. L. van Os. (*Ann. pharm. franc.*, 1954, **12**, 257.) Various parts of the rhizomes and roots of Chinese rhubarb cultivated at Buitenpost (Holland) were analysed chemically for their content of free and combined anthraquinone and anthranol compounds. At first fresh material was analysed directly but it was found that if the sliced material was dried rapidly at 50° C. there was no significant alteration in the analytical figures, apart from that due to reduction in bulk. Consequently dried material was used throughout for this investigation. It was shown that the young roots as well as the young wood of old roots were richer in free anthraquinones than the remainder of the underground parts, and the author suggests that the free anthraquinones are initially formed in the young roots and then deposited in the older parts in the form of glucosides. The amount of total anthraquinones is least in the pith and seems to be greatest where cambial activity is greatest; this may explain why varieties of rhubarb having star spots in the pith are always more highly esteemed than those without them. Slices of the vertical rhizome and roots at different levels were also analysed and as a result it was decided to use the quantity of combined anthraquinones (of which at least one half should be rhein compounds) in slices from the upper and lower parts of the rhizone and from the old wood of the roots as a criterion of quality in selection experiments. A further factor considered was the richness of cambial formations. So far not more than one generation has been produced on the above basis but it is hoped to continue the work on further generations. J. W. F.

PHARMACOLOGY AND THERAPEUTICS

Acetylcholine Antagonists, Protection Against the Toxicity of Cholinesterase Inhibitors by. M. W. Parkes and P. Sacra. (*Brit. J. Pharmacol.*, 1954, **9**, 299.) The toxicity of anticholinesterases is in the main due to accumulation

of acetylcholine at three sites, viz. the neuromuscular junction, autonomic ganglia and post-ganglionic cholinergic sites. The part played by each of these was determined for neostigmine, tetraethylpyrophosphate (TEPP), 3-dimethylphosphatotrimethylanilinium methylsulphate (I), and 3-diethylphosphato-1-methyl quinolinium methylsulphate (II). This was done by blocking selectively the acetylcholine at muscarinic sites with atropine, at the neuromuscular junction with *d*-tubocurarine and at ganglia with hexamethonium. Combinations of the antagonists were also used. The drugs were injected into the tail veins of mice. Death always occurred within 20 minutes, but 1 hour was allowed before final count was taken. The degree of protection offered by the antagonist was estimated firstly from a comparison of the anticholinesterase toxicity curves before and after maximally protective doses of antagonist and secondly by determining the amount of antagonist (PD50) which halved the mortality of an LD80 of the anticholinesterase. By the first method, atropine and *d*-tubocurarine appeared to act independently against neostigmine and II; II was most susceptible to *d*-tubocurarine. For these two anticholinesterases combined protection by all three antagonists was high. TEPP and I, however, were antagonised more by atropine, but all the antagonists overlapped in their protection. With TEPP combined protection was low. The second method was less precise, but gave results essentially similar to the first. Low doses of neostigmine were more strongly antagonised by atropine. This difference and others occurring between the two methods may indicate variation of mode of action or distribution, with change in dose, of the anticholinesterase. G. P.

Acetylcholine, Effect of, on Properties of Isolated Rabbit Auricle. T. C. West, L. D. Turner and T. A. Loomis. (*J. Pharmacol.*, 1954, **111**, 475.) This paper is concerned with the effect of acetylcholine on the refractory period, conduction time, contractile force and excitability in the isolated rabbit auricle and also its role in the production of auricular arrhythmias. The isolated auricles were stimulated electrically using a dual square wave stimulator, and records of electrical phenomena were obtained on a recorder, from electrodes placed on the right auricle near the sinus and on the left auricle. Acetylcholine caused a significant decrease in the spontaneous rate, force of contraction and duration of the refractory period; but no significant change in threshold intensity or conduction time. Acetylcholine also increased excitability. The occurrence of ectopic beats, when the interval between paired stimuli neared the refractory period, was increased by acetylcholine; which implied that the shortened refractory period aided the precipitation of such rhythms, particularly circus movement. G. F. S.

Analgesic Drugs, Miotic Effect in Evaluating. H. F. Fraser, T. L. Nash, G. D. Vanhorn and H. Isbell. (*Arch. int. Pharmacodyn.*, 1954, **98**, 443.) Measurements of the miotic effects are useful in evaluating potent analgesics. Experiments have been carried out in human volunteers (former morphine addicts) to correlate miotic effects with analgesic activity, side effects and addiction liability, using a number of morphine-like analgesics. Control observations were made before the administration of the drugs, given orally or subcutaneously. The observations were repeated at intervals up to 72 hours. Records were made of "euphoria," the incidence of adverse side effects such as pallor, nausea, vomiting, perspiration, excessive sedation and untoward mental effects. Pupil size, recorded photographically by electronic flash after 15 minutes in the dark and before analgesic medication, was considered 100 per cent. for each

subject. The degree of miosis due to the analgesic was calculated as a percentage of the control observation, and drugs and placebos were administered once a week in a randomised order. Time action curves were plotted for each drug and the areas under the curves measured with a planimeter. There was a significant difference in the response to 10 and 20 mg. of morphine, but not with 20 and 30 mg. There was a marked difference in the response to a series of compounds related to morphine. The (+)-form of 3-hydroxy-*N*-methylmorphinan (dromoran) and the 3-methyl ether were inert, while the (−)-form was very active. Morphine was much more active subcutaneously than orally. In a series of compounds related to methadone there was a considerable difference in potency. Most striking was the prolonged action of the methadols and acetylmethadols, the miotic effects persisting up to 72 hours. Pethidine at a dose of 160 mg. had only a slight effect on the pupil. Dilaudid had a strong effect, while 3-ethylmethylaminol-1:1(2′-dithienyl) but-1-ene and 6-methyl-$\triangle$-6-desoxymorphine were only short acting. Pupillary constriction correlated well with respiratory depression and side actions. There was also a very high correlation between pupillary constriction and the relief of abstinence in addicts. Unfortunately, measurements of miotic effects do not correlate well with measurements of the degree and duration of pain relief in man, but the method is useful in evaluating single doses of analgesic drugs when used in conjunction with other procedures and for assaying possible cumulative effects. G. F. S.

Barbiturate Antagonism. F. H. Shaw, S. E. Simon, N. Cass, A. Shulman, J. R. Anstee and E. R. Nelson. (*Nature, Lond.*, 1954, **174**, 402.) β-Methyl-β-ethylglutarimide (designated NP13) has been shown to be a barbiturate antangonist. At dose levels of 100 mg./kg., NP13 reduced the sleeping time of rats and mice under the action of pentobarbitone. NP13 itself at dose levels of 15 mg./kg. caused convulsions and at increased doses was fatal. Cats similarly were aroused to a state of reflex activity and semiconsciousness from pentobarbital narcosis. In this respect the effects were similar to those in humans, though in admixture with thiazole NP13 has been used to terminate the coma in some 20 cases of barbiturate poisoning. NP13 acts as a stimulant on barbiturate depressed respiration and is effective orally as well as by intravenous and intraperitoneal routes. Experiments are described which demonstrate the action of NP13 as barbiturate antagonists in the rabbit and dogs. 2:4-Diamino-5-phenylthiazole also reverses the narcotic effects of pentobarbitone, though it is less effective than NP13. The action of the latter is synergised by this particular thiazole derivative, which also counteracts the convulsive effects of NP13. J. B. S.

Benethamine Penicillin. M. G. Nelson, J. M. Talbot and T. B. Binns. (*Brit. med. J.*, 1954, **2**, 339.) Benethamine penicillin, the *N*-benzyl-β-phenylethylamine salt of penicillin, is a white, crystalline compound, very slightly soluble in water. It has a potency of approximately 1100 units/g. It is prepared as an aqueous suspension ready for injection in a vehicle containing suspending, buffering, wetting and bacteriostatic agents. It is slightly less toxic than procaine penicillin, when injected intravenously or subcutaneously into mice and rats. In terms of blood levels benethamine penicillin falls between procaine penicillin and benzathine penicillin, that is, the levels are lower and more prolonged than those obtained with procaine penicillin, but higher and of shorter duration than those following the injection of benzathine penicillin.

33 adult bed patients were given a single intramuscular injection of 300,000 units; 12 patients received 600,000 units and 10 patients 900,000 units. The difference in the results of the three doses was surprisingly small, but on the whole the penicillin blood levels of the patients who received the larger doses were somewhat higher and more prolonged. Thus, at 72 hours, 9 (27 per cent.) of 33 patients who received only 300,000 units had serum concentrations below 0·03 unit/ml., but none of the 22 patients on the higher doses had levels below this figure at either 72 or 96 hours. These results suggest that for the more sensitive and accessible infections seen in everyday practice one injection, or possibly two, of 600,000 units for an adult, or 300,000 units for a child, should be adequate treatment. It is unsuitable for the treatment of infections requiring a high concentration of penicillin, for which sodium penicillin remains the preparation of choice. It is best administered by deep intramuscular injection into the buttock or thigh, where it is less likely to provoke reaction than in the arm. S. L. W.

Bradikinine, Further Observations on. J. R. Pereira. (*Arch. int. Pharmacodyn.*, 1954, **98**, 484.) Further evidence is presented that bradikinine, a substance isolated from blood plasma after the addition of snake venom, owes its physiological activity to histamine. Bradikinine was obtained from a solution of casein in sodium hydroxide by treatment with jararaca (Bothrops jararaca) venom, and extracting with boiling ethanol. After filtration the ethanolic solution was evaporated *in vacuo* and the residue dried with acetone. A solution of the residue in distilled water caused a slow contraction of the guinea-pig isolated intestine; while the residue, after dissolving in glacial acetic acid and precipitating with ether, gave a positive Pauli's reaction and caused a powerful contraction of the guinea-pig intestine. The residue treated with sodium hydroxide and trichloracetic acid also contracted the intestine. Snake venom therefore liberated from casein a spasmogenic factor with pharmacological properties like histamine. Bradikinine was also obtained from the euglobulin fraction of horse plasma by treatment with snake venom. The chromatographic analysis of bradikinine, submitted to the extraction processes of Barsoum and Gaddum, and Hanke and Koessler, conclusively demonstrated the presence of histamine. It is suggested that the activity of all other "slow reacting substances" owe their spasmogenic activity to histamine. G. F. S.

Cinchophen and Acetylsalicylic Acid in Anticoagulant Treatment. S. Jarnum. (*Scand. J. clin. Invest.*, 1954, **6**, 91.) Cinchophen is contraindicated during the course of anticoagulant therapy as it may produce a severe fall in the already low prothrombin concentration. A case is recorded of a man under treatment with anticoagulant therapy for coronary thrombosis who was given cinchophen (4 g. in 48 hours) for an attack of gouty arthritis. He developed nausea and vomiting, and the prothrombin content fell to under 5 per cent. of normal. The next morning the patient had hæmatemesis, and in spite of repeated blood transfusions and treatment with vitamin K he died 20 hours later. Carefully controlled experiments on three patients with coronary thrombosis undergoing anticoagulant therapy confirmed the fall in prothrombin concentration following administration of cinchophen. Trials on a further 5 patients in which acetylsalicylic acid was used instead of cinchophen showed that when taken in doses of 1 to 3 g. daily acetylsalicylic acid does not present any great risk when used in combination with anticoagulant therapy. S. L. W.

Nalorphine, Effect of, on Dogs Anæsthetised with Pentobarbital Sodium. A. Vivante, F. F. Kao and J. Belford. (*J. Pharmacol.*, 1954, **111**, 436.) Nalophine is known to antagonise respiratory depression from morphine but against barbiturates its value is doubtful. Experiments carried out in 17 dogs, under pentobarbital anæsthesia, have shown that 30 mg./kg. of nalorphine (very high dose) intravenously significantly increased the respiration rate, the total ventilation and the ventilation equivalent for oxygen. Nalorphine also stimulated respiration in dogs under a chloraloseurethane mixture. A study of the mechanism of action suggested a central action on the respiratory centre and not through an indirect action of hypotension on the peripheral chemoreceptors of the cerebral cortex. G. F. S.

Phenylindanedione, Mode of Action of. W. Walker and R. B. Hunter. (*J. clin. Path.*, 1954, **7**, 249.) It is now accepted that at least three factors influence the clotting time in the one-stage prothrombin test, namely, factor V, factor VII (proconvertin) and prothrombin itself. The object of this study was to determine which of the factors is principally affected by phenylindanedione. It was shown that phenylindanedione administration results in a reduction of both prothrombin and factor VII. With therapeutic doses the prothrombin deficiency is not of sufficient degree to influence coagulation, and therefore the principal and most important site of action of phenylindanedione is factor VII. It was demonstrated that blood thromboplastin regeneration is impaired when phenylindanedione serum is used as a source of factor VII, and it is considered probable that the clinical results with phenylindanedione and the coumarin type anticoagulants are due to this and not to the effect on prothrombin. S. L. W.

Posterior Pituitary Hormone, Effect of, on the Release of Adrenocorticotrophic Hormone. S. Itoh and A. Arimura. (*Nature, Lond.*, 1954, **174**, 37.) Adrenaline causes a smaller depletion of ascorbic acid in adrenals of rats which have been injected with pituitary posterior lobe extract or have been dehydrated. These experiments show that depletion due to adrenocorticotrophic hormone is not affected by pituitary extract and suggest that the exogenous posterior pituitary hormones inhibit the release of the adrenocorticotrophic hormone from the anterior pituitary gland. Only the pressor fraction had this action. G. F. S.

Rauwiloid, Cardiovascular Effects of, in the Dog. J. T. Gourzis, R. R. Sonnenschein and R. Barden. (*Proc. Soc. exp. Biol. N.Y.*, 1954, **85**, 463.) The effects of hypotensive doses of rauwiloid, a mixture of alkaloids from the root of *Rauwolfia serpentina*, have been studied on the cardiovascular responses of normal dogs. 15 dogs were treated orally for 5 days at a dose level of 0·5 mg./kg./day and a further 15 kept untreated as controls. Eleven of the 15 treated dogs appeared to be depressed. On the sixth day the dogs were anæsthetised with pentobarbital sodium and the arterial blood pressure recorded. The treated dogs showed a significant decrease in the mean arterial pressure and heart rate. The pressor response to adrenaline was augmented and the hypotensive cardioaccelerator effects of *iso*propylnoradrenaline were enhanced. The blood pressure rise evoked by hypoxia was reversed and the carotid sinus reflex diminished. There was a blockade of the primary blood pressure rise due to faradization of the afferent vagus, which may indicate interference with sympathetic activity somewhere in the brain stem, but the secondary rise remained unaltered. The hypotensive responses to acetylcholine, histamine and efferent vagal stimulation were unaltered. G. F. S.

***Rauwolfia hirsuta*, Pharmacology of.** K. Mezey and B. Uribe. (*Arch. int. Pharmacodyn.*, 1954, **98**, 273.) This paper describes the chemistry and pharmacological effects of the alkaloids of the root of *Rauwolfia hirsuta*, called "rautensin". Two alkaloids have been isolated, one shown not to be rauwolfin but possibly rauwolcin, and the other found to be alstonin. Rautensin is slowly absorbed orally and only slowly excreted. The intraperitoneal LD50 in mice is 73 mg. per kg. and in rabbits the intravenous LD50 approximately 56 mg. per kg. Death is due to respiratory depression. A solution of 10 mg./ml. does not irritate the pupil. The main circulatory effects in the anæsthetised cat and dog are a fall in blood pressure, electro-cardiographical changes and bradycardia after intravenous doses of 1 to 2·0 mg. per kg. The fall in blood pressure is immediate, intensive and lasts several hours. Respiration is slowed and the heart slowing is partly inhibited by atropine. There is no alteration in the response to adrenaline but after two hours there is an inhibition. The electrocardiograph of the dog, after 4 mg./kg., shows at first a bradycardia, bifidity of the T wave and depression of the S.T. segment. After 15 minutes there are extra-systoles and tachycardia. The isolated toad heart shows a slowing of the heart with a 1 in 100,000 solution, reversible after washing. A 1 in 5000 solution decreases the amplitude of the rhythmic contractions of the rabbit isolated intestine. There are no effects on skeletal muscle and it does not interfere with glycæmia. G. F. S.

***Rauwolfia serpentina* in Treatment of Hypertension.** W. R. Livesey, J. H. Moyer and S. I. Miller. (*J. Amer. med. Ass.*, 1954, **155**, 1027.) Alseroxylon (rauwiloid) alone and with hydralazine or hexamethonium was tried in 84 out-patients with hypertension of varying degrees of severity. The patients had been under observation for from 2 months to 2 years before the trial, and were included only if the average control blood pressure was greater than 150/100 mm. of mercury or the mean blood pressure 115 mm. The criterion for responsiveness was a fall of at least 20 mm. in the average mean blood pressure or a reduction below 150/90 mm. When a second drug was added and the patient had responded previously to a single drug, an additional fall of 10 mm. in the average mean blood pressure or a return to the normotensive range was considered a response. Dosage of alseroxylon, which was given by mouth, was 2 mg. 4 times a day initially, corresponding in activity to about 125 mg. of the crude root. The dose was gradually increased to about 16 to 24 mg. daily or even up to 32 to 40 mg. For long term treatment the dose was lowered to about 16 mg. In 21 patients the drug was given in conjunction with hydralazine, and in 39 patients in conjunction with hexamethonium. 20/43 patients treated with alseroxylon alone obtained a significant reduction in blood pressure; 10/20 became normotensive. The impression was gained that the drug is less likely to be beneficial in cases with severe hypertension. Side effects were never severe; they included nasal congestion, slight drowsiness, increased appetite and weight gain, a sense of well-being and increased bowel movement but not diarrhœa. 11/43 patients who had not responded to alseroxylon alone were given hydralazine in addition in daily amounts of 100 to 1000 mg. in 4 divided doses. 8 responded but only 1 became normotensive. 4 who were responsive to alseroxylon alone gave a further response when hydralazine was given in addition. 4/9 patients unresponsive to combined treatment were unable to tolerate hydralazine. 36/39 patients were responsive to alseroxylon and hexamethonium, the latter compound being given in doses of 125 mg. or more 4 times daily, 2/8 with malignant hypertension failed to show improvement. For patients with severe hypertension combined admini-

stration of alseroxylon and hexamethonium is considered to be an effective treatment which produces few side effects. H. T. B.

Reserpine, Cardiovascular and Renal Hæmodynamic Response to. J. H. Moyer, W. Hughes and R. Huggins. (*J. Amer. med. Sci.*, 1954, **227**, 640.) The cardiovascular and renal hæmodynamic responses to reserpine when given intravenously to dogs were determined, and also the renal hæmodynamic response of hypertensive patients when given the drug orally and intravenously. In the experimental animals 3 to 4 mg. given intravenously usually produced after a variable lag period of 1 to 2 hours a moderate reduction in blood pressure lasting 2 to 5 hours. In one-fourth of the animals no significant effect on blood pressure was produced. The drug did not have a consistent effect on cardiac output. Renal hæmodynamics and electrolyte excretion rates were not altered significantly. Of the patients given reserpine intravenously, 4/6 showed some reduction in blood pressure and in one of them the reduction was excessive, necessitating the injection of noradrenaline. The average delay in the onset of the effect was 92 minutes, and the maximum effect occurred in about 3 hours. The effects on renal hæmodynamics were inconsistent. Of 8 patients given the drug by mouth for 3 months, 6 showed a significant reduction in blood pressure. Renal blood flow, glomerular filtration rates and renal excretion of water and electrolytes were not altered. There was no evidence of renal toxicity or depression of renal function. The hypotensive activity of the drug is only moderate. H. T. B.

Reserpine in the Treatment of Hypertension. W. Hughes, E. Dennis, R. McConn, R. Ford and J. H. Moyer. (*J. Amer. med. Sci.*, 1954, **228**, 21.) Clinical trials were carried out on reserpine, one of the alkaloids extracted from the root of *Rauwolfia serpentina*, with a view to ascertaining how far it is responsible for the therapeutic effectiveness of the root and its extracts in the treatment of hypertension. In the oral trials, reserpine was given by mouth to 62 unselected out-patients after a preliminary period of observation during which the patients were given placebos. The initial dosage was 2 mg. per day in divided doses after each meal and at bedtime. If excessive sedation occurred the dose was decreased for a time. If no reduction in blood pressure occurred the dose was increased to a maximum of 6 mg. per day. Intravenous administration was tried in 17 unselected patients, the dose being 1 to 3 mg. in 100 ml. of 5 per cent. aqueous dextrose injected during 15 to 30 minutes. Blood pressures and pulse rates were recorded every 5 to 10 minutes for 5 to 6 hours after the injection. 15 of the patients received one dose only. Of the patients taking the drug by mouth 29/62 followed for 2 months showed a significant reduction in blood pressure but the drug is only of moderate potency. Prolongation of treatment did not increase the proportion of patients who responded and of 47/62 followed for 2 to 7 months, only 24 showed a significant effect. The response is slow in onset and may not be apparent for 7 days; it is not increased by raising the daily dose above 2 mg. The most frequent and troublesome side effect was nasal congestion. About one-half of the patients experienced an increase in appetite and consequential gain in weight. Drowsiness and loss of initiative and energy were common but their frequency and severity diminished as the period of treatment increased, showing that the hypotensive activity is not due to sedation. Almost one-fifth of the patients complained of dizziness. 13/17 patients given reserpine intravenously showed a significant reduction in blood pressure 1 to 4 hours after administration, half of them becoming normotensive. Intravenous use requires further investigation.

H. T. B.

Suxamethonium in the Treatment of Tetanus. A. T. T. Forrester. (*Brit. med. J.*, 1954, **2**, 342.) The powerful, rapid and short-lived action of suxamethonium would appear to make it the most useful muscular relaxant drug for the control of reflex spasms of tetanus. It can rapidly overcome the severest convulsions, while full respiration and muscular power will return soon after it is withdrawn. In the case described, the patient, a man aged 42, was given a dose of the drug (by continuous intravenous infusion of a 0·2 per cent. solution) of 1·5 to 3 mg./minute for 5½ days, with additional larger doses in times of difficulty; a total of 22·5 g. was given without toxic side-effects. For much of the time spontaneous respiration was so reduced that oxygenation had to be artificially maintained. Light anæsthesia was maintained with nitrous oxide for most of the time; this produced restful sleep without any apparent untoward effects, but whenever it was withdrawn consciousness would return in a few minutes. Adequate bronchial drainage was ensured by frequent aspiration through a tracheotomy tube, and by a high angle of tip. S. L. W.

Tea, Effect on Gastric Secretions and Motility. C. W. Wirts, M. E. Rehfuss, W. J. Snape and P. C. Swenson. (*J. Amer. med. Ass.*, 1954, **155**, 725.) The object of this study was to determine the effect of tea on digestion and to evaluate the mechanism by which it produces relief of simple post-prandial distress. Some 300 intubation studies were performed on 114 persons over an 18-month period; all the patients had either an inactive duodenal ulcer or functional gastro-intestinal disorder. On the occasion of each examination the patient was given 2 cups (about 300 ml.) of sweetened tea, and, as a control, each test was repeated on the same patient on a different day substituting water for tea. It was found that tea appears to increase the rate of gastric emptying, when compared with the effect of an equal quantity of water, when used with a 40 per cent. protein, carbohydrate, fat, or combined meal. Iced tea (or water) has a more pronounced effect in this respect than hot tea. Tea appears to stimulate gastric motility, as shown by the amount of gastric residue remaining after various meals with tea and water both by tube and fluoroscopy as well as by the use of the intragastric balloon with the beverages alone. Tea exerts approximately the same effect on the gastric secretory output as water (volume *p*H, free acid, and pepsin). Taken as a beverage in average amounts, tea need not be contraindicated in the treatment of most gastro-intestinal conditions.

S. L. W.

Tetracycline, Clinical and Pharmacological Studies on. W. S. Waddington, G. G. Bergy, R. L. Nielsen and W. M. M. Kirby. (*J. Amer. med. Sci.*, 1954, **228**, 164.) Tetracycline was administered by mouth or by intravenous injection to 108 patients suffering from a variety of infections (bacterial pneumonia, urinary tract infections, and acute phases of chronic pulmonary infections). The antibiotic was given by mouth in the form of hard or soft capsules or enteric-coated tablets in a dose of 0·25 or 0·5 g. 6-hourly. For intravenous administration 0·5 g. of tetracycline was dissolved in 200 ml. of 5 per cent. dextrose solution and injected over a 30-minute period; alternatively, 0·5 g. dissolved in a litre of dextrose solution was administered slowly over 6 hours. The stability of tetracycline in aqueous solution was similar to that of oxytetracyline at temperatures ranging from − 20° to 25° C.; at 37° C. it appeared somewhat more stable than oxytetracycline. Serum concentrations of tetracycline were quite low following initial doses of 0·25 or 0·5 g. by mouth but rose subsequently, reaching a maximum after the 2nd to 4th dose. High levels were obtained with the administration of 0·5 g. intravenously over

(ABSTRACTS *continued on page* 152.)